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#9

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Applicants: Dr. Rudolf Falk
Dr. Samuel S. Asculai
(Now assigned to Hyal Pharmaceutical Corporation)

Title: THE USE OF HYALURONIC ACID OR ITS DERIVATIVES TO ENHANCE DELIVERY OF ANTINEOPLASTIC AGENTS

Inventors: Dr. Rudolf Falk,
Dr. Samuel S. Asculai

Examiner: Dr. Kathleen K. Fonda, Ph.D.

Group Art Unit: 1806 Extended Due Date: September 5, 1996

The Commissioner of Patents
UNITED STATES PATENT OFFICE
2011 Jefferson Davis Highway
Crystal Plaza 2, Room 1B03
Arlington, Virginia
U.S.A. 22202

DECLARATION OF EVA TURLEY
under § 1.132

I, EVA TURLEY, make oath and say as follows:

1. I am the same Eva Turley who filed the Declaration dated September 4, 1996 in the prosecution of the above-identified application.

2. THE OFFICE ACTION

For the purposes of preparing this Declaration, I was asked to review the Official Action Summary issued by the Patent Office, identified as paper #33, and

particularly the objections to the specification relating to the breadth of the claims which read on methods of treating:

(a) an arbitrary disorder or condition;

(b) cancers generally;

(c) side effects of drugs; and

(d) AIDS.

With regards to this ground of objection, the Examiner in the action states that there has been no disclosure adequate to enable the entire scope of these claims in the specification as filed. I note the statement in the action quotes "Significantly no declarant has stated that the instant invention would be expected to be broadly useful to treat any condition whatsoever". I will comment upon this statement in my declaration.

I have also been asked to comment about the dosage amount being indefinite having regard to the use of the expression "10mg/70kg person and 1000mg/70kg person".

I have also been asked to discuss the expression "dose excess" and the Examiner's statement that the expression "of dosage excess" having regard to what is normally understood by persons skilled in the art is not sufficient to the Examiner. According to the Examiner, this was not convincing because without knowing the intended result of administration of component (1), it would not be possible to determine when a dose excess had been reached.

Additionally, I was also made aware of the rejection of the Examiner of the dosage claims for the composition based on the Della Valle (U.S. Patent 4,736,024) and the rejection of the Examiner of both the dosage claims and methods of

treatment claims based on what I am advised by Ivor Hughes was the obviousness of the subject matter of the claims based on the reading together of Seifter et al (U.K. Patent 769287) read in view of Schultz (U.S. Patent 4,808,576) and Della Valle (U.S. Patent 4,376,024) {sic} (I believe the Examiner meant U.S. Patent 4,736,024) as further evidenced by Balazs in the article "Hyaluronic acid: Its Structure and Use", Cosmetics & Toiletries, Polymers in Cosmetics 1984; 99: 65-72.

I understand from page 7 of the action that, according to the Examiner, Della Valle's suggestion of dermatological preparations would provide ample motivation for one of ordinary skill in the art to alter the amount of hyaluronic acid present in the composition.

With respect to the method claims the Examiner states that the prior art relied upon by the Examiner does indeed suggest to do what Applicants have done. According to the Examiner it was not relevant that the Applicants may have discovered a particular advantage to the suggested method which may not have been recognized by prior workers in the field.

3. REPRESENTATIVE CLAIMS

With this Official Action, I was also given a copy of what I was advised by Ivor M. Hughes are representative proposed claims, a copy of which I attach as **Exhibit 1** to this my declaration. For the purposes of this declaration, I have been advised by Ivor Hughes that the Applicants filed the first application for this invention in September 1989 in Canada and filed a PCT application which enlarged the disclosure of the original case which had effect in the United States as if filed in the United States on September 18, 1990 and which claimed priority from the Canadian Application.

4. STATE OF THE ART

In this section I discuss the state of the art with respect to the use of forms of hyaluronan and what was known to persons skilled in the art at the time of filing of the Canadian Application in September 1989 and the PCT application filed in September 1990. Where possible I have referred to articles which particularly point out the point that I wish to make. In making the points I have referred to the references cited by the Examiner in the Official Action. Because the reference had been cited previously, I may have referred to it in my earlier declaration. I provide these additional comments. If not previously discussed, I discuss it now.

U.K. Patent specification 769287 (Seifter et al) does not, in my opinion, relate to hyaluronic acid. Hyaluronic acid is, by definition, a polymer. At best, Seifter is a structure which is not a form of hyaluronic acid (i.e. not a polymer) but is an oligosaccharide. Seifter is not generally known to persons skilled in the art and even though the invention refers to partially depolymerized hyaluronic acid as a spreading and lipemia-clearing agent, Seifter's product would not act as hyaluronan. In fact, one of the references relied upon by the Examiner, hyaluronic acid, its structure and use in polymers in cosmetics by Balazs et al (Volume 99, June 1984, Cosmetics and Toiletries) states that:

> "It is not expected that even very short chains (oligosaccharides) of degraded hyaluronic acid that contained more than 5 to 10 disaccharide units can pass through this layer of the skin." (See page 71 of the said reference.)

Seifter thus is meaningless with respect to the teachings of the use of hyaluronic acid with medicines or treatments involving the use of hyaluronic acid with

medicines. The comments of Dr. Fraser in his earlier declaration which I examined in detail are, in my opinion, accurate.

Where forms of hyaluronic acid have been used topically, they have been taught to provide films on the eye (for example, U.S. Patent 4,736,024, Della Valle) and films on the skin (U.S. Patent 4,808,576, Schultz). However, there was no expectation of any transport or delivery of any medicinal or therapeutic agent by the use of hyaluronan in the prior art. Where it was to be applied onto the skin it was expected to dry up and flake off. It was not known to penetrate into the skin or to transport anything into the skin. In fact, Schultz in U.S. Patent 4,808,576 taught at column 6, lines 1 to 9:

> "without the transdermal carrier the sodium hyaluronate applied was ineffective"

Of particular importance is the statement at column 12, lines 14-18:

> "The hyaluronate solution simply evaporated to dryness leaving a film on the skin of the subject" (column 12, lines 14 to 18).

These statements are consistent with what was known at the time in the art (both before Della Valle and after Della Valle). When hyaluronic acid was topically applied it was not expected to penetrate and did not penetrate using the prior art formulation. The dosages were expected to evaporate to a dry, flaky film product. This was what was thought would happen and, in fact, did appear when dosage amounts containing hyaluronan were applied topically.

The eye is not like the skin. Persons skilled in the art thought the skin to be a barrier. Della Valle did not teach the use of hyaluronan with keratonized

skin. The skin was expected by persons skilled in the art to be a barrier. The eye is covered by a moist membrane. Skin was not like that at all. One cannot predict that the application of "a drop" to the eye can translate to an effective composition being useful for the skin when a larger dosage (a "larger drop") is applied to the skin (where it is expected to dry up and flake off) or to mucous membranes (where it would be diluted and washed away).

This is clear from a number of references:

(a) U.S. Patent 3,887,703 which issued in 1979 teaches in examples 13, 14, 15 and 17 combinations of mucopolysaccharides (which include hyaluronan), together with medicines. Drops of this solution were applied. The drops would each contain much less than 1mg of the form of hyaluronic acid. Persons skilled in the art would expect that whatever was applied would sit there and dry up and flake off.

(b) U.S. Patent 4,141,973, which issued February 27, 1979 teaches high molecular weight forms of hyaluronic acid (molecular weight exceeding 750,000 daltons and preferably greater than 1,200,000 daltons). At column 14, Balazs indicates that the high molecular weight form of hyaluronan can be used as a vehicle for any kind of intra-articular medication to protect the articular cartilage from the possible harmful effects of the particular drug used and to prolong the effect of the drug by decreasing its diffusion out of the articular space. To me and to persons skilled in the art this teaching means that the combination of the form of hyaluronan having the high molecular weight, together with the, for example, corticosteroid is injected into the intra-articular space and because of the high molecular weight of the hyaluronic acid the effect of the drug is prolonged by decreasing (delaying) its diffusion out of the articular space providing a retard effect. This is a retard effect. The high molecular weight hyaluronan remains in

the intraarticular cavity and the medicine (for example, corticosteroid) leaches therefrom and is absorbed.

(c) In the article found in "Polymers", in Cosmetics and Toiletries, Vol. 99, June 1984, entitled "Hyaluronic Acid, Its Structure and Use", at page 71 Balazs et al state:

> "The stratum corneum is known to be impermeable to molecules as large as hyaluronic acid."
>
> "Therefore, it is not expected that even very short chains of oligosaccharides of degraded hyaluronic acid that contain more than 5 to 10 pentisaccharide units can pass through this layer of the skin. There is no evidence in the literature that any hyaluronic acid - in any solvent or with any added carrier - will penetrate deeper than the crevices between the desclimating cells."

These statements were made in 1984.

(d) This statement is a precise statement of what was known to persons skilled in the art. Persons skilled in the art did not expect, prior to 1989 that hyaluronic acid would penetrate the skin. Therefore, when the Examiner has concluded that Della Valle's patent (U.S. Patent 4,736,024) suggests the use of dermatological preparations and that this reference would provide ample motivation for one of ordinary skill in the art to alter the amount of hyaluronic acid present in the composition, she is, in my opinion, mistaken. There would be no reason for anyone to modify Della Valle because the dermatological preparations would not work. They would only have been expected to dry up and flake off if applied topically. For a chemical to be an effective vehicle for drugs, the vehicle must

target. Hyaluronan was not expected to be an effective vehicle for the skin or mucous membrane.

(e) Thus, because of what would have been expected by persons skilled in the art at the time, even with the teachings in U.S. Patent 4,736,024, and particularly, at column 1, line 48-53, where Della Valle states it is possible to obtain films on the corneal epithelium which are homogeneous, stable, perfectly transparent and which adhere well, guaranteeing prolonged bioavailability of the drug thereby forming excellent preparations with a retard effect means that a film is provided from which the medicine leaches and which film provides a retard effect, thus prolonging the time the medicine is present before release to be absorbed by the corneal epithelium or the other areas such as the mucous membrane, such as the mouth or be absorbed by transcutaneous re-absorption, for example from suppositories, discussed at column 2, lines 52-64. However, the use is premised by Della Valle on the specific advantages of the combinations which is not only discussed at column 1, lines 46-53, but also at column 2, lines 45-51 and column 30, lines 57-68. These advantages are as discussed above in this subparagraph (e).

(f) It is therefore clear that persons skilled in the art would only expect a film to form from the teachings of U.S. Patent 4,736,024 or from the teachings of the other references which were discussed earlier and would be expected to dry up and flake off.

(g) Thus, the Examiner's conclusions with respect to the methods of treatment of Della Valle is also, in my opinion, incorrect. Della Valle does not indeed suggest to do what Applicants have done because in Della Valle the motivation is not provided to prepare dermatological compositions which would sit on the skin and penetrate because it was known and expected that such dermatological skin formulations would not penetrate. They would dry up. I, as

an expert with respect to hyaluronan, would not have concluded and have not concluded as the Examiner has concluded, that Della Valle taught what the Examiner asserts Della Valle teaches. The eye is not the skin. It is one thing to apply a "drop" on the eye. It is another to apply the "same drop" or a "larger drop" on the skin (where it was expected to dry up and flake off) and mucous membranes (where it was expected it would be washed away).

(h) U.S. Patent 4,711,780, issued December 8, 1987, a copy of which I also enclose as **Exhibit 2**, discusses the use of hyaluronic acid in formulations in reproductive tract treatments using mucopolysaccharides. Two of the mucopolysaccharides are condroitin sulphate and hyaluronic acid which are preferred for the treatments in the reproductive tract. The mucopolysaccharide, according to the inventors, acts as a barrier, thereby preventing toxins on the skin surface from penetrating into the blood circulation system which otherwise leads to septicemia (see column 5, lines 25-28). A number of formulations are provided (see examples 4, 5 and 6) dealing with the reproductive tract which may contain, according to the teachings of the patent, hyaluronic acid. However, the hyaluronic acid acts as a barrier and in this regard high molecular weight hyaluronic acid was known for acting as a barrier which I understood the hyaluronan in this patent to be. No teaching or use or methods are taught which show the use of hyaluronic acid for transportation purposes of the invention. The molecular weight taught in the patent is understood by me to be high molecular weight hyaluronic acid.

While Della Valle discussed quantitative ratios by weight of the two components extending over a vast ratio range (column 8) and while Della Valle also discussed concentrations at column 9 this does not mean that Della Valle appreciated the benefits of Applicants' invention. In my experience the eye is substantially different from the skin. I would not have used the teachings of

Della Valle to make dermatological preparations. In 1989 I thought that hyaluronan was so hydrophilic that it would dry up and flake off and there would be no benefit to the skin. Thus, there would be no motivation from the words of Della Valle to prepare dermatological preparations because persons skilled in the art would believe that any dosages prepared would be useful (they would, when applied, dry up and flake off and not be expected to permit the dosage amount of the medicine to be absorbed). Additionally, there is no teaching in Della Valle nor any suggestion to teach the use of intravenous or intramuscular or injectible formulations and the use thereof for the treatment of disease because all of Della Valle's teachings relied on the finding that the formulations provided films which are homogeneous, stable, perfectly transparent and which adhere well guaranteeing prolonged bioavailability of the drug thereby forming excellent preparations with the retard effect - in other words, formulations that permit the medicine to leach therefrom but which persons skilled in the art would have been expected to dry up and flake off.

I have had in excess of 20 years in this area and I must say I am very surprised by the Examiner's conclusions. There is no evidence in the literature that I am aware of prior to 1989 that permits her to arrive at this conclusion. I have read all of the references referred to by the Examiner and they do not teach either singly or in combination with one another, use or (in my opinion as a person skilled in the art) the claimed dosages and methods of treatment using those dosages.

(i) The Examiner also referred to Schultz (U.S. Patent 4,808,576). As previously described however, Schultz does not teach combinations of hyaluronan and medicine and does not teach the use of medicines being combined with the hyaluronan. The hyaluronan is the medication and by the internal delivery system of the body when injected into the body, finds its way to

the site where it could be used in the same way that if diclofenac were injected into the body it too would find its way to the site in need of treatment to provide pain relief because of diffusion throughout the body. It is clear that if applied topically, Schultz (U.S. Patent 4,808,576) teaches that there must be a transdermal carrier present such as DMSO or propylene glycol (see column 6, lines 1-9). Without the transdermal carrier the hyaluronan is ineffective and would simply evaporate to dryness leaving a film on the skin of the subject (see column 12, lines 14-17). In other words, the film would flake off.

(j) I have also been given a copy of an article entitled "Effect of Several Penetration Enhancers on the Percutaneous Absorption of Indomethacin in Hairless Rats", Chem. Pharm. Bull. 36(4), 1519-1528(1988). In that article there is a discussion of the effect of several penetration enhancers on the percutaneous absorption of drugs. Note the use of the expression "percutaneous absorption". In other words the medicine is absorbed through the skin and the penetration enhancers enable such absorption. One of the compounds tested is sodium hyaluronate and the clinicians found that it had no enhancing effect on the skin permeation of indomethacin.

Thus, all the articles that I have referred to provide no motivation for making either topically applied dosage amounts of formulations or intravenous, subcutaneous, injectible or the like dosage amounts of formulations which are administered onto/into the body by the use of minimum amounts of 10mg of hyaluronic acid having a molecular weight less than 750,000 daltons together with an effective dosage amount of a therapeutic agent because the prior researchers did not appreciate that forms of hyaluronan transport the medicine and such persons did not appreciate that such formulations, for example Della Valle with respect to dermatological formulations, were viable. There was no motivation to produce such formulations.

Even to this date, the use of hyaluronan in the eye in small drops has been tested by Dr. Ian Constable and the result published in Round Table Series #40, 1995. In this article, a copy of which is attached as **Exhibit 3** to this my declaration, Professor Constable discusses the administration of drops of hyaluronan and NSAIDS in the eye. He clearly states at page 141:

> "It does not get to the back of the eye. Available data on combining hyaluronic acid with drugs in drops show rapid clearance from the anterior chamber period. Available data on combining hyaluronic acid with drugs in drops show rapid clearance from the anterior chamber. Dr. Gustafson has published data on receptors in the corneal epithelium and nothing gets to the back of the eye if administered as drops."

This is even in 1995.

5. I have carefully reviewed the teachings in the PCT application which entered the National Phase in the United States Patent Office as I am advised by Ivor Hughes, Patent Agent, under Application Serial Number 07/675,908 and the claims attached as **Exhibit 1** to this my declaration. The claims are of two types. The first type are, I understand, representative of dosage amounts of compositions containing minimum amounts of forms of hyaluronan of 10mg having a maximum specified molecular weight together with an effective amount of a therapeutic agent. The second type of claim is the method claim using the dosages in the treatment of underperfused tissue and/or pathological tissue. It is not that the therapeutic agent is new, rather it is the dosages which are new that provide enhanced transport of the agent to the site in need of treatment.

6. It is not every disease or condition which, on my understanding of the application the invention can be used. As described at page 24, beginning at line 13, the combination of the hyaluronic acid in the appropriate dosage amounts (greater than 10mg when administered), together with the drugs or other therapeutic agents produces an unusual targeting for underperfused tissue and/or pathological tissue. This is the specific area to which the invention relates. In other words, where the treatment involves underperfused tissue and/or pathological tissue, the form of hyaluronan targets the underperfused tissue and/or pathological tissue with the drug/therapeutic agent/medicine which is used to treat the underperfused tissue and/or pathological tissue. The application then lists throughout its disclosure a substantial number of conditions and diseases which can be treated by the invention and which involve, according to the teachings of the patent, underperfused tissue and/or pathological tissue. Representative of the conditions and diseases which involve underperfused tissue and/or pathological tissue are specified in Claim 6. These conditions and diseases that have been listed are not inclusive of all conditions and diseases involving underperfused tissue and/or pathological tissue. They are, however, representative according to the teachings of the application.

7. As I understand the expression underperfused tissue and as is confirmed by the teachings in the application at page 24, underperfused tissue involves tissue, such as a kidney, which is underperfused or malfunctioning due to insufficient intravascular volume (see page 24, lines 31-33). The tissue being underperfused is therefor underperfused with respect to blood.

8. Pathological tissue includes underperfused tissue. Pathological tissue involves tissue which pertains to or results from being attacked by a disease or condition which destroys the tissue or changes it from its normal condition.

Pathological tissue also arises where a pathological change is caused to occur in the tissue. Underperfused tissue will inevitably be hypoxic which will result in necrosis of the tissue, a pathological change. A pathological change, if not reversed, will cause necrosis of tissue. Even transient underperfusion, followed by reperfusion, will lead to pathological changes.

When tissue is underperfused and hypoxic, a point is eventually reached when the capillaries become more permeable. This pathological change to the tissue would then facilitate the delivery of the form of hyaluronan associated with the drug into the affected tissues (in addition to the effect of the hyaluronan). Thus, as tumors need blood vessels and capillaries for the transportation of blood into the tumor and because the blood vessels and capillaries to the tumours are defective there is bleeding in the tumour and these blood vessels, because of their permeability enable delivery of the form of hyaluronan and the medicine.

9. Since the writing of the application, much has been learned with respect to the causes of the unusual alteration of the drugs' distribution and performance in the human body and the production of the unusual targeting for underperfused tissue and/or pathological tissue. Today, we know that such tissue generally expresses excess hyaluronan receptors which causes the form of hyaluronan administered to target such underperfused and/or pathological tissue. This is discussed in a number of articles that have now been published and may even be discussed in a number of later patent applications. Two of such articles were published in the Second International Workshop on hyaluronan drug delivery and the Third International Workshop on hyaluronan and drug delivery which were published in or about 1995 and thereafter. One article is entitled "Targeting of Hyaluronan to Tumours Via Binding to ICAM-1" (ICAM-1 is not, we have now discovered, a hyaluronan receptor; however, there are other

receptors such as RHAMM and CD-44). Another such article is entitled "Role of Hyaluronan Receptors in Breast Carcinoma". I attach copies of the articles as Exhibit 4 and 5 to this my declaration. The point is that the application teaches that the combination is now targeting to the pathological tissue, even when administered by the systemic intravenous route (page 25, lines 29-31).

10. Additionally, when the amount of hyaluronan exceeds 200mg in the dosage, the toxic side effects which usually occur with NSAIDS, such as gastro-intestinal distress, neurological abnormalities, depression, etc., even at elevated amounts of the NSAID, indomethacin, are reduced. As each patient would be affected differently the reduction of the side effects would vary. Some persons would have the side effects eliminated and others the side effects only reduced. The point is, however, that it is the combination of the hyaluronic acid at the minimum amount of 200mg and the drug which causes the reduction of the side effects.

It is thus the minimum amount of 10mg of the hyaluronic acid which enhances the transportation and delivery to the underperfused and/or pathological tissue. The differentiation between all tissue and underperfused and/or pathological tissue is not made in the prior art. There is not even any discussion. Therefore, no undue experimentation to determine the diseases and conditions generally need be ascertained. If underperfused tissue and/or pathological tissue is involved, then persons skilled in the art will understand that this invention applies to such tissue and can be used with such tissue in the treatment thereof. The claims as now presented to me reflect my comments above and, in my opinion, the subject matter thereof is clearly and unequivocally taught in the application. The conditions and diseases listed are all specified in the application. More broadly, the pathological tissue and/or underperfused tissue to which they all relate is also described. The dosage amounts all relate to

medicinal agents and therapeutic agents in therapeutically effective amounts to treat the disease or condition involving underperfused tissue and pathological tissue.

11. These dosages, but for Applicants' invention, for treating the methods would not have been developed by persons skilled in the art because there was no reason to develop such dosages. For example, the fact persons skilled in the art would not use Della Valle's teachings to provide dermatological dosages because persons skilled in the art would expect the form of hyaluronan to dry and flake off. This drying and flaking off would have directed persons skilled in the art in other directions from developing Applicants' formulations. United States Patent 4,808,576 is to the same effect.

It is thus clear that Applicants' dosages are not taught by the prior art.

Thus, with respect to paragraph 8 of my declaration referencing the particular disorders to be treated, the application does not relate to any arbitrary disorder or condition. Cancers generally involve pathological tissue and having regard to the number of different cancers treated successfully in the application, Applicants have clearly taught that the invention can be applied to all cancers because they involve pathologic tissue. The different cancers described in the application are:

Cancers	*Examples*
Laryngeal Epidermoid	Case I, page 36
Malignant Melanoma	Case II, pages 36-37
Cancer of the Gallbladder	Case III, page 38
Cancer of the Colon Metastatic to the Liver	Case IV, pages 38-39
Transitional Cell Cancer of the Bladder	Case V, pages 39-40
Right Upper Lobe Lesion	Case VI, pages 40-42

Cancer of the Breast	Case VII, pages 42-45 Case XI, pages 47-48 Case XIV, pages 50-51
Tumour in the Right Upper Lobe of the Lung	Case VIII, pages 45-46
Gastric Cancer	Case IV, pages 46-47
Hepatoma	Case X, page 47
Leomyosarcoma of the Uterus	Case XIA, page 48
Inguinal Recurrent Melanoma	Case XIB, pages 48-49
Stomach Cancer	Case XVII, page 52
Colon Cancer	Case XVIII, pages 52-53 Case XX, page 54
Carcinoma of the Lung	Case XIX, pages 53-54
Cancer of the Uterus	Case XXI, page 54
Adenocarcinoma	Case XXII, pages 54-55
Intraperitoneal Tumor	Case XXIII, pages 55-56
Carcinoma of the Pancreas	Case XXIV, page 56 Case XXV, page 56
Carcinoma of the Ovary	Case XXVIII, pages 57-58
Epitheloid Sarcoma	Case XXXI, pages 58-59
Gastric Cancer	Case XXXII, pages 60-61
Carcinoma of the Cervix	Case XXXVII, pages 64-65

With respect to the side effects of drugs, the application discusses and exemplifies the reduction of side effects of an NSAID at pages 25 and 26 (and in the cases). However, the comments are equally applicable to other drugs where they do have side effects because, first of all, drugs which are now being targeted to a site in need of treatment would not go to other areas where the side effects could be exhibited. For example, a drug going to the liver directly and not going to the stomach where the side effects cause problems would eliminate these side effects. Thus, the administration of hyaluronic acid with anti-neoplastic agent which has side effects such as nausea to the patient, the patient will be, in my opinion, less nauseous because of the specific targeting discussed in the application at page 24.

Finally, with respect to AIDS, the Applicants have exhibited an example involving AIDS - AIDS involves pathological tissue. Further, the body suffers

from other diseases caused by the attacks of the immune system by the HIV virus. Thus, persons suffering from AIDS suffer from other diseases and Example 40 discusses the patient being diagnosed with AIDS having the undetermined neoplastic disorder in the lungs. At that point when the patient has full blown AIDS, the patient has underperfused and/or pathological tissue which will be capable of being treated using Applicants' invention.

12. With respect to the expression "dosage amount", the claims do not now include a reference to a 70kg person. However, the reference to a 70kg person remains in the application and as I understand the application, the 70kg person is a representative person to whom the proposed dosages will be delivered.

13. With respect to a dosage excess, component (1) (the agent) would be required to be known in order to determine whether or not the dose of the medicine is a dosage excess. However, when dealing with the treatment of diseases and conditions, persons skilled in the art will realize a dosage excess means an excess amount of what is normally used for that condition or disease.

14. Having previously discussed the state of the art and the teachings of the application, it should now be clear that the claims are now free of the prior art previously commented upon. The Examiner has rejected the claims to dosages under 35 U.S.C. §103 as being obvious over Della Valle and the same claims and the method claims as being obvious over Seifter in view of Schultz and Della Valle as evidenced by the Balazs article.

In my opinion, the dosage claims that are presently before me and attached to my declaration as **Exhibit 1** are not obvious over the Della Valle reference because there is no motivation to make the dosages for topical use because persons skilled in the art would believe that the dosages would not be useful -

persons skilled in the art would believe in 1989 that they would dry and flake off without effect. Applicants' dosages would not, therefore, exist but for the fact of Applicants' unique methods of treatment because there would be no other reason to make them. Thus, with respect to the rejection of the method and dosage claims based on Seifter, Schultz, Della Valle and Balazs, Seifter does not relate to hyaluronic acid as is clear from Dr. Fraser's earlier statements in his Declaration, Schultz is not suitable for topical use of hyaluronic acid by itself and Della Valle does not provide any motivation to make the dosages or carry out the methods. In fact, the Balazs article states that topically there is no evidence in the literature that any hyaluronic acid in any solvent, or with any added carrier, will penetrate deeper than the crevices between the desquamating cells. This was in 1984. The position had not changed by 1988 by the issuance of Schultz (U.S. Patent 4,808,576) or by the issuance of Della Valle (U.S. Patent 4,736,024) where persons skilled in the art would have expected the dermatological preparations to have dried up, flaked and dropped off. This position is confirmed in the 1988 article discussed in paragraph 4(j) of my declaration. Factually, the Examiner is in error with respect to her conclusions. There is no motivation in Della Valle or any reference, either alone or together with others, to develop the methods of treatment as taught by Applicants, nor is there any motivation to teach the dermatological preparations that are used in the methods of treatment. Applicants' dermatological preparations are obvious. The dermatological preparations did not exist. Furthermore, the combination of the form of hyaluronic acid (having a minimum amount of 10mg) together with an agent which is suitable for use to treat underperfused and/or pathological tissue is not taught. There is no teaching of Applicants' methods and thus the dermatological preparations in the prior art. There is no teaching of the treatment of underperfused and/or pathological tissue.

15. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements will jeopardize the validity of the application and any patent issuing thereon.

EXECUTED this 20 day

of June, 1997.

EVA TURLEY

EXHIBIT 1

IN THE CLAIMS

1. A dosage amount of pharmaceutical composition in a suitable pharmaceutically acceptable excipient therefor comprising:

(1) an agent selected from a medicinal agent and a therapeutic agent and combinations thereof in a therapeutically effective amount to treat a disease or condition involving underperfused tissue and pathological tissue in humans;

and (2) a form of hyaluronic acid selected from the group consisting of hyaluronic acid, pharmaceutically acceptable salts thereof and combinations thereof, characterized in that said dosage amount of said composition

(a) is in a dosage form which is suitable for administration in humans;

and (b) is in a form in which (i) component (1) is in an effective dosage amount to treat said disease or condition by penetration at the site to be treated; and (ii) component (2) is immediately available to transport component (1) from the point of administration to the site to be treated, and which component (2) is in an effective non-toxic amount to facilitate the transport of component (1) upon administration from the site of administration to the site in need of treatment, through the tissue, at the site to be treated and through cell membranes into individual cells to be treated, wherein said amount of component (2) is sufficient to provide a dosage of between 10mg and 1000mg of component (2) and wherein the molecular weight of component (2) is less than 750,000 daltons and greater than 150,000 daltons.

2. A dosage amount of a pharmaceutical composition in a suitable pharmaceutically acceptable excipient therefor comprising an agent selected from a medicinal agent and a therapeutic agent and a form of hyaluronic acid, the improvement comprising that the dosage amount of the composition is suitable for treating a condition or disease involving tissue selected from the group of

underperfused tissues and pathological tissue in a human, wherein a therapeutically effective amount of the agent selected from the medicinal agent and the therapeutic agent and combinations is provided in combination with an effective amount of a form of hyaluronic acid selected from hyaluronic acid, pharmaceutically acceptable salts thereof and combinations thereof sufficient to facilitate transportation of the agent to the site to be treated through the tissue and cell membranes into individual cells to be treated, wherein said amount of the form of hyaluronic acid is present in an amount of between 10mg and 1000mg of the form of hyaluronic acid, and wherein the molecular weight of the form of hyaluronic acid is less than 750,000 daltons and greater than 150,000 daltons.

3. A dosage amount of a pharmaceutical composition in a suitable pharmaceutically acceptable excipient therefor for treating a disease or condition involving tissue selected from the group of underperfused and pathological tissue in a human comprising an effective amount of an agent selected from a free radical scavenger, ascorbic acid, Vitamin C, an anti-cancer agent, chemotherapeutic agent, anti-viral agents, non-steroidal anti-inflammatory drugs (NSAIDS), steroidal anti-inflammatory drugs, anti-fungal agent, detoxifying agents, analgesic, bronchodilator, anti-bacterial agent, antibiotics, drugs for the treatment of vascular ischemia monoclonal antibody, diuretics, immunosuppressants, lymphokines, α and β interferon, insulin, estrogen, progestogen, anti-metabolites, calcium channel blockers, drugs for the treatment of psoriasis and combinations thereof to facilitate the agent's penetration through tissue including scar tissue, at site to be treated, through cell membranes into individual cells to be treated, wherein said amount of the form of hyaluronic acid is sufficient to provide a dosage between 10mg and 1000mg of the form of hyaluronic acid and wherein the molecular weight of the form of

hyaluronic acid is less than 750,000 daltons and greater than 150,000 daltons, with the proviso that if the agent selected is phloretin, it is solubilized.

4. A method of treating a condition or disease involving tissue selected from the group of underperfused tissue and pathological tissue in a human who will benefit from the treatment by the administration of an agent selected from a medicinal agent and a therapeutic agent, the method comprising administering to the human a therapeutically effective dosage amounts of a pharmaceutical composition in a suitable carrier therefor for such time as required, each dosage amount comprising an effective amount of the agent to treat the disease or condition involving tissue selected from underperfused tissue and pathological tissue and a sufficient amount of a form of hyaluronic acid selected from hyaluronic acid, pharmaceutically acceptable salts and combinations thereof sufficient to transport the agent from the site of administration to the site in need of treatment and facilitate penetration of the agent through the tissue, at the site to be treated through cell membranes into individual cells to be treated, wherein said amount of the form of hyaluronic acid is present in an amount between 10mg and 1000mg of the form of hyaluronic acid, and wherein the molecular weight of the form of hyaluronic acid is less than 750,000 daltons and greater than 150,000 daltons.

5. A method of treating a disease or condition in a human who will benefit from the treatment with a combination of an agent selected from a medicinal agent and a therapeutic agent and a form of hyaluronic acid, the improvement comprising the administration of an effective dosage amount of a composition to treat the disease or condition which involves tissue selected from underperfused tissue and pathological tissue, said dosage amount comprising an effective amount of an agent selected from a therapeutic agent and a medicinal agent to treat the disease or condition and a form of hyaluronic acid selected from the

group consisting of hyaluronic acid, pharmaceutically acceptable salts thereof, together with suitable excipients and combinations thereof in an effective amount sufficient to transport the agent from a site of administration to a site in need of treatment and facilitate penetration of the agent at the site to be treated through the tissue, through cell membranes into individual cells to be treated, wherein said amount of said form of hyaluronic acid is present in an amount between 10mg and 1000mg of the form of hyaluronic acid and wherein the molecular weight of the form of hyaluronic acid is less than 750,000 daltons and greater than 150,000 daltons.

6. A method for the treatment of a disease and condition involving underperfused tissue and pathological tissue in humans selected from the group consisting of a neoplastic condition, abscess, acne, AIDS, arthritis, auto-aggressive diseases, Berger's disease, brain trauma, bronchodilation, canker sore, chronic bacterial infection, chronic fungal infection, connective tissue diseases, Crohn's Disease, degeneration, diabetes, disease carried by a virus, edema, epitheloid sarcoma, balding, heart patient (cardiac), herpes, shingles, hypertension, implants, infection, inflammatory conditions, malfunctioning kidney, kyphosis, lameness, leomyosarcoma, leukemia, malnutrition, massive injury, mesothelioma, metastatic disease (in the liver), mononucleosis, neoplasia, pain, post-menopause, prostaglandin synthesis, psoriasis, renal failure, respiratory difficulties, retroviruses, swelling, vascular ischemia and cardiac insufficiency, said method comprising administration of at least a dosage amount of a pharmaceutical composition in a suitable pharmaceutically acceptable excipient therefor, each dosage amount comprising a therapeutically effective amount of an agent selected from the group consisting of a medicinal agent and a therapeutic agent and combination thereof in a therapeutically effective amount to treat the disease and condition and a sufficient amount of a form of hyaluronic acid selected from the group consisting of hyaluronic acid, salts thereof and

combinations thereof to facilitate delivery and penetration of the agents to the site to be treated by the agent passing through tissue including scar tissue, through cell membranes into individual cells to be treated, wherein said amount of the form of hyaluronic acid is sufficient to provide a dosage between 10mg and 1000mg of the form of hyaluronic acid and wherein the molecular weight of the form of hyaluronic acid is less than 750,000 daltons and greater than 150,000 daltons.